Acute Hepatitis in Malaria

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Background

Malaria is endemic in 91 countries and approximately 40% of the world population is at risk of acquiring the infection. However, malaria is not a common cause of acute hepatitis.[1] We describe a case of malaria and acute hepatitis in a patient who presented to our institution complaining of abdominal pain and fever.

Case

A 42-year-old man presented to the emergency department with a 5-day history of fever, chills, and epigastric pain and a 1-day history of vomiting. The patient had no comorbid conditions. He had come from Haiti 5 days prior to presentation and described a history of possible mosquito bites.

The patient denied alcohol abuse, previous blood transfusions, and unprotected sex. A physical examination was notable for low-grade fever, icteric sclerae, and epigastric tenderness. The laboratory tests were relevant for bandemia, thrombocytopenia, and a raised serum creatinine level of 1.6 mg/dL (Table 1). His liver profile was consistent with hepatitis and hyperbilirubinemia (Table 2). The possibility of malaria was considered based on the clinical presentation and the fact that the patient had come from an area in which malaria is endemic. The diagnosis of malaria was confirmed on a Wright stained peripheral smear, which revealed bodies within some erythrocytes consistent with *Plasmodium falciparum*. Treatment was started with an initial dose of 600 mg of oral chloroquine followed by 300 mg 6 hours later and on days 2 and 3 of treatment in the hospital. Autoimmune, viral, and metabolic causes of acute hepatitis were excluded by confirming negative antinuclear and antismooth-muscle antibodies, negative hepatitis A and B serologies, negative hepatitis C virus RNA, and normal ceruloplasmin. Alpha-1-antitrypsin and ferritin and iron saturation were within normal limits. The hospital course was notable for further increase in the activity of transaminases; however, the patient experienced symptomatic improvement and was discharged 5 days after admission in stable condition. His laboratory tests indicated a downward trend of the

Table 1. Complete Blood Count

	WBC, 10^3/mL	Bands, %	Hb, g/dL	HCT, %	Platelets, 10^5/mL
Day 1	5.59	45	15.2	47.4	46
Day 2	9.29	35	15	44.9	43
Day 3	10.6	13	14.3	43.2	72
Day 4	11.1	0	13.7	40.9	72
Day 5	12.80	0	13.2	40.2	119
Day 12	6.98	0	12.9	41.5	521

WBC = white blood cells; Hb = hemoglobin; HCT = hematocrit.

Table 2. Liver Profile

	AST, IU/mL	ALT, IU/mL	Alkaline Phosphatase, IU/mL	Total Bilirubin, mg/dL
Day 1	196	129	84	5
Day 2	350	211	110	5.4
Day 3	406	284	108	4.2
Day 4	305	241	150	4.8
Day 5	292	238	166	4.1
Day 12	40	80	88	1

ALT = alanine aminotransferase; AST = asparate aminotransferase.

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activity of the transaminases as well as serum bilirubin and creatinine concentrations. One week after discharge, follow-up laboratory tests revealed decreased transaminase activity and normal serum bilirubin level (see Table 2).

Discussion

Malaria is an uncommon cause of acute hepatitis. According to the World Health Organization (WHO), other than jaundice, signs of hepatic dysfunction are unusual and clinical signs of liver failure are rarely seen unless there is concomitant viral hepatitis including B and E.[1] In our patient, viral markers for hepatitis A, B, and C infections were negative.

Jaundice and renal failure are the most common systemic manifestations of malaria. Jaundice is mostly due to unconjugated hyperbilirubinemia secondary to intravenous hemolysis[1]; however, there are reports from Asia of hepatitis with evidence of hepatic encephalopathy and conjugated hyperbilirubinemia.[2,3] Liver histology reveals hepatocyte necrosis, cholestasis, and granulomatous lesions with malarial nodules.[2] The liver function abnormalities are not reported to be related to the grade of parasitemia, fever, duration of illness, nutritional status, or associated medical problems. The term malarial hepatitis has been used to describe this condition.

Patients with severe malarial hepatitis usually have a poor prognosis, characterized by a high incidence of renal failure, acute respiratory distress syndrome, and septicemia, with a mortality rate as high as 40%.[4] The mechanism suggested to explain liver insult is ischemia, resulting from an alteration in blood flow through the liver as infected red blood cells (RBCs) adhere to endothelial cells, blocking the sinusoids.[5] Early recognition, as exhibited in this patient, and treatment of malaria should lead to quick reversal of liver abnormalities.

To our knowledge, this is the first reported case of malarial hepatitis treated in the United States. With the increase in travel between the United States and areas where malaria is endemic, recognizing malaria as a cause of acute hepatitis should lead to expeditious diagnosis and treatment.

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Review

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In 1898, tropical medicine pioneer Sir Patrick Manson wrote:

> Under the influence of a succession of acute attacks, hepatic congestion may acquire a more or less permanent character. If this be long maintained, it tends to bring about various kind and degree of chronic hepatitis with hypertrophy of the interlobular connective tissue, and in time it leads to hypertrophic or to different forms of atrophic and cirrhotic changes. Thus irremediable organic disease of the liver, portal obstruction, and ascites may ensue.

In 1913, Lucius Nicholls wrote, "Cirrhosis of the liver is a common condition of many tropical countries, and numerous authorities have asserted that some cases are caused by repeated attacks of malaria." Today, few clinicians, if any, would give credence to early work involving hepatitis and/or cirrhosis as long-term sequelae of *P. falciparum* infection; however, all agree with Sir Patrick's idea of hepatic involvement.

According to the WHO, jaundice is one of the cardinal manifestations of severe malaria in adults.[1] Causes contributing to jaundice may include destruction of parasitized RBCs leading to intravascular hemolysis, immune hemolysis due to the adherence of circulating antigen-antibody complexes to the surface of erythrocytes, malnutrition, shock, or disseminated intravascular coagulation leading to microangiopathic hemolysis and hepatic dysfunction. Liver damage may result from an alteration in vascular flow through the organ as the parasitized RBCs adhere to endothelial cells, blocking sinusoids and obstructing intrahepatic blood flow. Histopathological changes associated with malaria include steatosis, focal hepatocyte necrosis, cholestasis, bile stasis, granulomatous lesions, and malarial nodules.[1]

Intravascular hemolysis of parasitized and nonparasitized RBCs has been considered an important factor in the causation of mild to moderate jaundice, in which bilirubin is predominantly unconjugated. However, hemolysis is never the sole cause of severe jaundice nor the conjugated hyperbilirubinemia and increases in the serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are seen in many patients

with malaria. Many investigators have proposed a role for cholestasis and hepatocellular damage in patients with malaria.[2-11]

Severe jaundice associated with *P. falciparum* malaria is now a well-known entity, and high incidences are being reported in many parts of Southeast Asia. According to the WHO, serum bilirubin levels in patients with severe falciparum malaria remain in the range of 7–10 mg/dL but in a recent study 29 out of 86 patients had serum bilirubin levels greater than 10 mg/dL with a maximum value of 48.2 mg/dL observed.[2] Another study found 14 of 31 patients with serum bilirubin levels greater than 14 mg/dL with predominantly conjugated hyperbilirubinemia.[3] According to the WHO, apart from jaundice, signs of hepatic dysfunction are unusual and clinical signs of liver failure with hepatic encephalopathy, such as liver flaps or asterixis, are never seen unless there is concomitant viral hepatitis.[1] Lately, however, there have been reports showing evidence of hepatic encephalopathy from different parts of world, including India.[2,4-6]

The pathogenesis of hepatitis or cholestasis in malaria is unclear. Devarbhavi and colleagues[4] studied 25 patients with fulminant hepatic failure in malaria and found that in most cases prothrombin time and liver span, which are prognostic markers of hepatic dysfunction and severity of disease, remained normal. This finding suggests that the synthetic function of the liver is preserved and abnormal liver function tests may be secondary to the release of various cytokines such as tumor necrosis factor α (TNF-α) and interleukin (IL)-10. This study and many others have shown that hepatocyte necrosis is either absent or spotty and cannot explain the marked increase in bilirubin level. Impaired excretion of bile secondary to loss of microvilli in bile canaliculi and local disturbance of blood flow in sinusoids have been suggested as causes of cholestasis and hepatocyte dysfunction. In addition, Kupffer cell stimulation along with endotoxemia and high levels of cytokines such as TNF-α, IL-6, and IL-10 may give rise to the hepatic, neurologic, and biochemical changes seen in severe malaria dysfunction. Aside from these factors, renal failure, hemolysis, shock, and sepsis may also play a significant role in hyperbilirubinemia. Moreover patients with severe hepatic dysfunction in malaria may not show evidence of impaired synthetic function, such as prolonged prothrombin time. Microscopic examination of the liver reveals hepatocyte necrosis, cholestasis, bile stasis, and focal accumulation of histiocytes forming nonspecific granulomatous lesions, sinusoidal dilatation, and congestion with Kupffer cell hyperplasia.[2,7-9]

A low and falling albumin level is an important index of hepatic dysfunction. Concentration of serum enzymes such as AST, ALT, and 5-nucleotidase may be moderately elevated. Prothrombin time may be moderately prolonged. Other abnormalities include lactic acidosis, hypoglycemia, changes in triglycerides, phospholipids, free fatty acids, cholesterol, and nonesterified fatty acids, as well as abnormal bromosulphthalein retention.[1]

The association of malarial hepatitis and hepatic encephalopathy has been very nicely described in Indian patients.[2,4,8] In a recent study of 190 adult patients with evidence of falciparum malaria, Kochar and coauthors observed that serum bilirubin levels ranged from 3 to 48.2 mg/dL (mean ± SD, 10.44 ± 8.71 mg/dL), AST levels ranged from 40 to 1,120 IU/L (mean ± SD, 294.47 ± 250.67 IU/L), and ALT levels from 40 to 1,245 IU/L (mean ± SD, 371.12 ± 296.76 IU/L).[8] Many of these patients had multiple organ dysfunction. Detailed ultrasonography done in 29 patients with serum bilirubin greater than 10 mg/dL revealed decreased liver echogenecity and increased gall bladder wall thickness in few patients, and no evidence of intrahepatic or extrahepatic bile duct dilation. These changes are similar to those observed in acute viral hepatitis. During the course of illness, 15 patients had evidence of hepatic encephalopathy diagnosed by intellectual deterioration, flapping tremors, electroencephalographic evidence of triphasic waves, background delta activity, pseudoperiodic burst suppression, and raised arterial blood ammonia level (120–427 mEq/L; mean ± SD, 310 ± 98.39 mEq/L). Histopathological examination revealed swollen hepatocytes, malarial pigment (hemozoin) deposition in reticuloepithelial cells, portal infiltration by mononuclear cells, Kupffer cell hyperplasia, intrahepatic cholestasis, and focal areas of necrosis.[2] Similar biochemical and histopathological changes were reported in a previous study in malarial hepatitis done at the same center.[8]

All of these changes have been reported in connection with *P. falciparum* infection, but recently jaundice and hepatic dysfunction have also been described in patients with *Plasmodium vivax* malaria.[12,13] Our group recently reported 11 cases of severe *P. vivax* malaria in Bikaner (western India) confirmed by polymerase chain reaction study.[12] Four of 11 patients had serum bilirubin levels greater than 3 mg/dL and two patients with jaundice had serum bilirubin levels of more than 10 mg/dL (16 mg/dL in one patient) along with cerebral malaria, renal failure, circulatory collapse, severe anemia, hemoglobinuria, abnormal bleeding, and acute respiratory distress syndrome. Aminotransferase levels were also raised, with AST and ALT levels up to 546 IU/L and 510 IU/L, respectively, noted.

Nautiyal and colleagues[13] recently reported a case of hepatic dysfunction in a patient with *P. vivax* infection. A 37-year-old man presented to the emergency department of a New York hospital complaining of high fever, chills, and rigors of several weeks. The patient was a US soldier

who had returned from Afghanistan 7 months earlier. On physical examination the patient had jaundice and peripheral blood examination revealed *P. vivax* infection. He was treated with quinine and doxycycline in usual doses and prompt recovery ensued. The authors stressed that with the increase in global travel, clinicians should consider malaria in a patient presenting with fever and jaundice.

The present case reported by Shoukier and colleagues may not be the first reported case of malaria with jaundice in the United States, but it is an important observation. The presentation of fever with jaundice is an important clinical symptom in tropical countries and malaria is one of the major causes of such combinations. Recognition of this combination of symptoms in connection with malaria is essential for every healthcare provider engaged in the treatment of patients who have traveled in countries where malaria is endemic. These two case reports may help in delivering immediate and meaningful treatment to such patients.

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